The concept is an old one, and was first put forward by Karl Pearson some 60 years ago, not long after the principles of Mendel's work were being rediscovered. Heritability estimates on this assumption are often surprisingly high, and this is of importance for the planning of research into the aetiology of these conditions.

Anencephalus and Spina Bifida

It is an indication of our increasing interest in these malformations that in the short time since anencephalus and spina bifida were last discussed in these columns several new reports are worth noting. A survey by K. M. Laurence, C. O. Carter, and P. A. David of over 100,000 births in the Vale of Glamorgan and the mining valleys of South Wales during the years 1956-62 provided details of 364 cases of anencephaly (some of them with spina bifida also) and 425 cases of spina bifida without anencephaly. There were also 46 cases of hydrocephalus not associated with spina bifida, but these will not be considered further because they appear to be quite distinct aetologically from the other two malformations.

The spina bifida rate (4.13 per 1,000) was the highest ever recorded in a population, and the anencephalic rate (3.54 per 1,000) has been exceeded only once in a population survey (in Northern Ireland). There were no significant fluctuations in the annual rates of these malformations, but there were some interesting regional variations, the incidence being highest in the east of the area and lowest in the west. This pattern contrasts sharply with that shown by the British Isles as a whole, where there is a marked downward gradient from west to east. The authors could not account for local variations in incidence by differences in geological formation, background radioactivity, or ethnic, sociological, or economic characteristics. The incidence was higher in urban than in rural areas, but within urban areas it did not seem to be related to population density.

A second paper by the same authors confirmed an earlier report from Birmingham that the incidence of both malformations is greater among first-born and among the offspring of young and old mothers. Paternal age seems to have no independent effect. The distribution of ABO and rhesus blood groups among the mothers was no different from that of the general population of the area. In South Wales, as in Birmingham, there was no social class gradient in the incidence of anencephaly. This is in contrast with experience in Scotland, where the families of unskilled manual workers have an incidence five times that of families of the professional and managerial classes.

The South Wales investigation, in common with most previous studies, provided evidence of familial concentration of these malformations. The incidence of anencephaly or spina bifida among the sibs of affected infants was 5.2%, which is nearly seven times the figure for the general population. In Liverpool the incidence among sibs (4.2%) was also between six and seven times the general population value, and in Birmingham, where these defects occur rather less frequently, the same ratio between incidence in sibs and population was observed. It seems then that the risk of recurrence is greater in some places than others and is related to the local incidence in the population. It has also been shown that in the same locality the risk of recurrence may vary with time and keeps in step with secular variations in the incidence among the general population. The malformation rate is greater for infants who have two previous sibs affected than for those with only one; in such families the risk to subsequent sibs may be as high as 1 in 10.

The South Wales data on twins are consistent with earlier reports on the rarity with which both members of a monozygous pair are affected. There were 13 pairs of twins, of which 9 were of the same sex. This suggests a normal representation of monozygous sets, but there was no instance of the defect in both twins. There was, however, one set of triplets in which both the female members were anencephalic, the third member of the set, a boy, being normal.

A useful analysis of a large twin series collected by S. Yen and B. MacMahon has recently been published. From the records of 1,793 cases of anencephalus and spina bifida born in hospitals in Rhode Island and Boston, they obtained data on 30 pairs, of which 23 were of like sex. In none of these were both members affected. By adding six other series from the literature to their own data they raised the total to 108 twin pairs. In every case only one member of the pair was affected. The fact that 73% of the pairs were of like sex suggested that there had been no selective loss of monozygous pairs. This evidence, coupled with that of a number of isolated reports, seems to leave no doubt that both twins rarely suffer from these malformations. In fact concordance is such an uncommon event that if a member of a twin pregnancy is affected the co-twin is less likely to be malformed than is a subsequent sib. Yen and MacMahon explored the possibility that this is due to the early abortion of twin pregnancies in which both members are affected, but found little supporting evidence.

We now know much more about anencephalus and spina bifida than we did 20 years ago, and various interpretations of the facts have been put forward. Few now believe that these malformations can be explained in simple genetic terms, and some geneticists now think that a polygenic mode of inheritance is responsible. But to accommodate the very strong body of evidence indicative of non-genetic aetiological influences they accept that the manifestation of these genes can be influenced by the intrauterine environment and that genetic mechanisms alone cannot explain the marked national variations in incidence shown for example by Northern Ireland, Wales, Scotland, England, and France. The familial evidence so far available is equivocal, but a careful unbiased study of half-sibs and of second- and third-degree relatives could be decisive and is badly needed. At present the most revealing evidence has come from twin studies. Unless this evidence has been seriously misinterpreted, the only genetic hypotheses with which it is compatible are as Yen and MacMahon have pointed out, ones involving low
penetrance. If this is so the genetic background of these malformations is not likely to be elucidated for a long time. It would be unfortunate if preoccupation with this relatively unimportant aspect of the problem distracted attention from the much more pressing need to identify the environmental influences.

Glycogen Storage Disease

S. van Creveld and E. von Gierke first reported the clinical and post mortem findings in the hepatoglycemic type of glycogen storage disease 40 years ago. Only in the last 15 years, however, have such cases, the symptomatology of which may be broadly similar, been differentiated into at least three types caused by congenital deficiencies of specific enzymes concerned in the breakdown of glycogen to glucose. These enzymes are glucose 6-phosphatase, amylo-1,6-glucosidase (debranching enzyme), and phosphorylase, deficiencies of which give rise, respectively, to types I, III, and VI glycogen storage diseases in the aetiological classification of G. T. Cori.

The term von Gierke's disease is now usually restricted to the type I disease, descriptions of which have appeared in many reviews. Abdominal enlargement is usually noticed in the first year of life and may be present at birth. Growth is markedly retarded, there is a tendency to adiposity, particularly of cheeks and breast, and eruptive xanthomata may occur. The massive enlargement of the liver, which often extends below the umbilicus, may give rise to pronounced lordosis, but portal hypertension and splenomegaly are rarely noted. Apart from carbohydrate metabolism hepatic function is usually unimpaired. Even when there is gross enlargement of the kidneys, with infiltration of the renal tubules by glycogen, surprisingly little abnormality of renal function may be detected, though glycosuria and non-specific aminoaciduria are sometimes noted.

Laboratory investigation shows marked fasting hypoglycaemia, often below 10 mg. true glucose/100 ml. blood, but clinical signs and symptoms of hypoglycaemia may be absent, and mental development is generally normal. Hyperlipidaemia is often so pronounced that compensatory volume corrections are necessary in the determination of plasma constituents. Acetaenemia and acetonuria, usually related to episodes of acidosis, may be present, and the blood lactate concentration is usually high and increases considerably after the administration of adrenaline or glucagon. Blood urate levels are often raised because of the reduced renal clearance for urate in the presence of persistent lactic acidosis, and this may lead to manifestations of gout in patients who survive for a long time.

Functional tests of carbohydrate metabolism may lead to a presumptive diagnosis by differentiation of the responses to be expected in the various hepatoglycemic types. The absence of a normal hyperglycaemic response to the glycogenolytic action of adrenaline or glucagon in the fasting state is usually found in all the hepatoglycemic types. Similar tests performed after a meal often help to differentiate types I and III, since feeding leads to the synthesis of new outer chains of glycogen, and these may give rise to a substantial increase in blood glucose after glucagon in type III disease, but will remain unavailable as glucose 6-phosphate in type I disease. A further test, particularly useful in the diagnosis of type I disease, relies on the conversion of infused galactose or fructose into glucose. Glucose 6-phosphatase is essential for this conversion, so that the absence of a hyperglycaemic response to the infusion of these sugars is a good indication of its absence.

These tests provide information that may lead to an almost conclusive diagnosis in certain cases, and they are particularly useful in suggesting the most important estimations to perform on the small amount of liver obtained by needle biopsy; but a complete definitive analysis covering glycogen content and structure and all relevant enzyme activities is often necessary, and this requires about 1 g. of tissue taken at laparotomy. Biopsy of muscle from the abdominal wall should be done at the same time for the investigation of muscular involvement in cases of type III disease. If they are frozen at once, muscle may be kept for months without deterioration of enzyme activities.

During recent years the use of blood cells for enzyme assay has provided an attractive alternative to surgical biopsy, and has provided opportunities for the biochemical investigation of modes of inheritance of these diseases. Thus leucocyte assays may detect the enzyme deficiencies in types III and VI, and the erythrocyte glycogen content is usually increased in these types. It has been reported that the glucose 6-phosphatase deficiency may be detected in intestinal mucosa obtained by peroral biopsy of patients with type I disease. This alternative to liver biopsy may find wider use in the future diagnosis of other types of glycogen storage disease.

With the recognition of the fundamental biochemical abnormalities of type I disease rational definitive therapy in infancy may ensure relatively long survival for these patients. Frequent small feeds of glucose-containing carbohydrate throughout the day and night protect against severe hypoglycaemia, and the early recognition and vigorous treatment of infection and acidosis can avert life-threatening crises.

Fellowships for General Practitioners

To get away for a few months' study leave in middle life can be a most refreshing experience for the professional man. Perhaps of no one is this truer than the general practitioner, tied as he often is by his livelihood to a particular locality. Recognizing this, the Nuffield Foundation is offering fellowships now of two to six months' duration to general practitioners, preferably between the ages of 35 and 45, to undertake approved study overseas during 1970 of some subject of importance to general practice. The scheme is run in co-operation with the Royal College of General Practitioners, and it includes financial provision of locum assistance in the practice. Details can be found on advertisement page xxxi.